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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,917	02/19/2004	Lesley Murray	PC23581	7562
28940	7590	10/19/2007		
PFIZER INC 10555 SCIENCE CENTER DRIVE SAN DIEGO, CA 92121			EXAMINER GEMBEH, SHIRLEY V	
			ART UNIT 1614	PAPER NUMBER
			MAIL DATE 10/19/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/780,917

Applicant(s)

MURRAY ET AL.

Examiner

Shirley V. Gembah

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 March 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15-64 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15-54 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The response filed **3/16/07** presents remarks and arguments to the office action mailed **11/16/06**. Applicant's request for reconsideration of the rejection of claims in the last office action has been considered.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of Claims

Claims 1-14 are cancelled and Claims 15-64 are pending. Claim 15 has been amended and claims 16-64 are newly added.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-34 and 45-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating osteoporosis, does not reasonably provide enablement for treating excessive osteolysis or cancer that has metastasized to the bones with compound of formula I. The specification does not

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enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

Nature of the Invention: The claims are drawn to a method of treating excessive osteolysis in a patient administering a compound of formula I (of 5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (compound 1) is enabled.

The nature of the invention is extremely complex in that the skilled artisan would not be able to determine what is defined by excessive osteolysis. At what point is osteolysis excessive? Which other compounds of formula I would be capable of treating the wide variety of disease encompassed by excessive osteolysis?

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Breath of the Claims: The complex nature of the claims is greatly exacerbated by the breath of the claims. The claims encompass treating many pathologies characterized by excessive osteolytic disease without defining what these osteolytic diseases entail following administration of a claimed compound of formula I.

Working Examples: The working examples provided by the specification are directed toward the synthesis of the various compounds, the treatment of inhibition of phosphorylation of colony stimulating factor 1 receptor (CSF1R), and inhibition of murine osteoclast, breast cancer and breast cancer metastasis. See specification pages 56-61.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual treatment of excessive osteolysis in a patient with the claimed compounds makes practicing the claimed invention unpredictable in terms of identifying diseases that are characterized by excessive osteolysis. The use of 5-(5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (compound 1) is enabled.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first determine at what point osteolysis becomes excessive, as well as compound dosages, duration of treatment, route of administration, and the appropriate animal model to determine whether or not the compound is effective for the particular osteolytic condition in a particular population.

Level of ordinary skill in the art.

The level of ordinary skill in the art is high. Hence, one of skill in the art must perform an exhaustive search to determine which diseases are associated with excessive osteolysis and what compounds of the instant claims are to practice the claimed invention.

Claims 55-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

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Nature of the Invention: Claims 55-64 are drawn to a method of treating excessive osteolysis in a patient that is post- menopausal comprising administering a compound of formula I.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual treatment of excessive osteolysis in a patient that is post-menopausal with the claimed compounds is not taught in the prior art and makes practicing the claimed invention unpredictable. There is no showing how the treatment is carried out.

Guidance of the Specification: The guidance given by the specification as to how one would determine how to treat post-menopausal patient is absent.

Level of ordinary skill in the art.

The level of skill in the art is high. Hence, the specification fails to provide any support of how treatment is carried out in a post-menopausal patient with the claimed compounds, thus necessitating one of ordinary skill in the art to perform an exhaustive search to determine which of the many compounds can be used in the treatment of post-menopausal patient.

The amount of Experimentation Necessary: In order to practice claimed invention, the skilled artisan would have to first determine when osteolysis becomes excessive in post-menopausal patients, compound dosages, duration of treatment, route of administration, etc., and the appropriate animal model to determine whether or not the compound is effective for the particular osteolytic condition in said population.

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The Examiner acknowledges that the Office does not require the presence of working examples in the disclosure; however, given the highly unpredictable state of the art and that Applicant does not provide sufficient guidance or direction as to how to make and use the full scope of the presently claimed invention without undue amount of experimentation, the Office would reasonably require further appropriate disclosure, possibly via examples commensurate with the scope of the present claims.

Claims 15-22, 25-32, 35-42, 45-52 and 55-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The definitions of the groups of Formula I encompass heteroaryl and/or heterocyclic ring systems. The number of structural variations is almost limitless. For example, binding to the colony stimulating factor 1-receptor would be affected by bulky R groups that would make it difficult for binding. Steric hindrance is another factor that affects the sensitivity of the receptor.

Applicant has not conveyed possession of the invention with reasonable clarity to one skilled in the art. In particular, Applicant has not provided a description of the structure of a representative number of derivative compounds, a description of the

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chemical and/or physical characteristics of a representative number of compounds nor a description of how to obtain a representative number of specific compounds.

To satisfy the written description requirement, applicant must convey with reasonable clarity to one skilled in the art, as of the filing date that application was in possession of the claimed invention. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); *In re Ruschig*, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

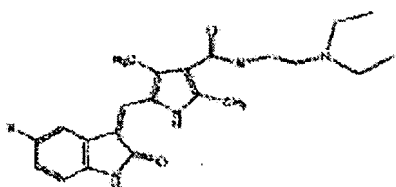
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

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under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15-34 and 35-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mendel et al., Clinical Cancer Research, Vol. 9, 327-337, 2003, in view of Tang et al., US 6,573,293. Goltzman J. Clin. Invest., 2001,107(10), 1219-1220, is provided as evidence.

Mendel teaches using a compound SU11248 (see Fig. I, page 328, rt. col.), which is the same compound required by instant claims 23-34

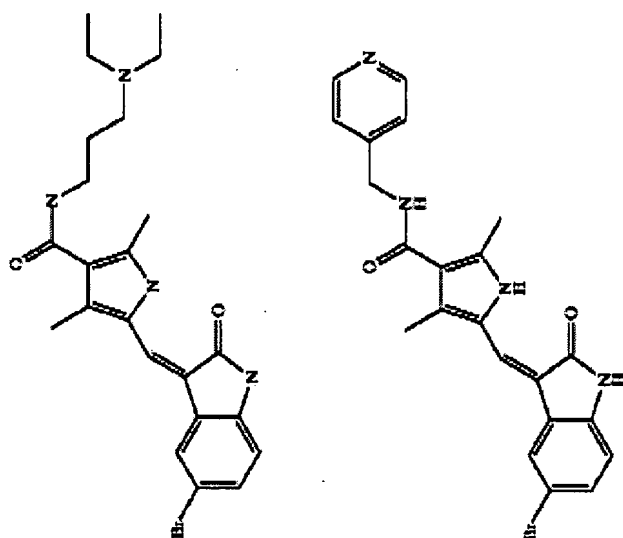


for targeting phosphorylation in tumor (see underlining abstract). As required by instant claims 15-34, the compound known as SU 11248 is encompassed in the claim language.

Tang et al. teach, administering compounds of formulae 1 and 2, as required by instant claims 23-24 and 33-34, to inhibit the proliferation of tumor cells (see col. 246,

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lines 45) and inhibit phosphorylation in tumors (see col. 61 and col. 64 compounds 71



and 74).

Tang et al., however, fail to teach the fluorinated form of the compound. One of ordinary skill in the art would have been motivated to use the fluoride as the halogen because fluorine is considered more reactive than bromine. Tang et al. teach the halogens used are either F, Cl or Br. Therefore, one of ordinary skill in the art would have been motivated to use either halogen and expect success in doing so.

One of ordinary skill in the art would have been motivated to use the compounds of the prior art and treat phosphorylation of colony stimulating factor 1 receptor in a patient because the compounds are known in the prior art to inhibit phosphorylation in tumors.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the above compounds for inhibition of phosphorylation and treatment of osteolysis in a patient with cancer because bone is a

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highly hospitable environment for colonization and growth of metastatic cancer/tumors, as evident by Goltzman, J. Clin. Invest. 2001, 107(10); 1219-1220.

One of ordinary skill in the art would have been motivated to do this because it is known in the prior art that the compounds recited above inhibits phosphorylation and inhibit tumor proliferation. Also, inhibitors of bone resorption thus appear all the more promising as tools to manage skeletal metastases, especially if they can be introduced early in the course of cancer therapy. Therefore, one of ordinary skill in the art would be motivated to use a drug that will inhibit cancer that has metastasized to the bone because of the known fact taught by Goltzman that tumors that metastasized to the bone must occupy a space within the bone matrix. Thus treating cancer will effectively treat or inhibit bone osteolysis. Based on the teachings of the above prior art claims 35-54 are *prima facie* obvious.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of

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ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembel whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SVG 
10/02/07



**PHYLLIS SPIVACK
PRIMARY EXAMINER**